mated for calculation of the trial sample size. Finally, it should be noted that the adjusted mean difference in IIEF-6 scores was 3.9 points in favour of NeuroSAFE, which is just below the minimum clinically important difference of 4 points suggested by previous studies [3].

In conclusion, the authors should be commended for conducting this RCT. While results from this type of study represent the cornerstone of evidence-based medicine, we believe that several issues should be addressed before considering NeuroSAFE RARP as standard of care for patients with localised PC, especially in light of the longer surgical time and higher costs associated with this technique.

Conflicts of interest: The authors have nothing to disclose.

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Re: Local Anaesthetic Transperineal Biopsy Versus Transrectal Prostate Biopsy in Prostate Cancer Detection (TRANSLATE): A Multicentre, Randomised, Controlled Trial

Bryant RJ, Marian IR, Williams R, et al

Lancet Oncol 2025;26:583–95

Expert's summary:

Bryant et al [1] report results from the TRANSLATE randomized controlled trial (RCT) of local-anesthesia transperineal (TPBx) versus transrectal (TRBx) prostate biopsy. The trial was powered to show a 10% difference (55% vs 45%) in favor of TPBx for detection of clinically significant prostate cancer (PC), defined as International Society of Urological Pathology grade group (GG) ≥2 cancer. Final analysis for 1126 patients revealed a 6% higher detection rate with TPBx (60% vs 54% for TRBx), which did not meet the prespecified endpoint of a 10% difference [2]. Nonetheless, the difference was rated statistically significant because of the high overall detection rate.

Expert's comments:

At present, treatment of PC—unlike other genitourinary malignancies such as renal cancer—is exclusively performed after a biopsy with histological confirmation of cancer. TRBx has been recommended for decades, as it is easy to perform and most PC tumors are located in the dorsolateral part of the prostate.

On the basis of a 2020 UK retrospective cohort analysis of approximately 100 000 TPBx and 387 000 TRBx cases that showed a significantly lower rate of infection and sepsis with TPBx (0.53% vs 0.31%; $p < 0.001$; confidence interval [CI] 99%) [3], the European Association of Urology changed their recommendation to TPBx (strong recommendation). The main concern regarding TRBx was the slightly higher rate of sepsis (five vs three of 1000 patients). However, three recent RCTs were not able to show a significant advantage of TRBx with regard to infection and sepsis [4–6]. TRANSLATE was not designed to detect differences in infection rates. The frequency of patient-reported complications was higher in the TPBx arm (454 vs 436 for TRBx; odds ratio 1.23, 95% CI 0.93–1.65); only 1% in both arms experienced sepsis, with no significant difference. However, TPBx was significantly more bothersome. The difference in GG 2 PC detection of <6% is not clinically relevant to deciding in favor of TPBx.

Patient-reported side effects are very important. In all the relevant RCTs, the absolute number of serious complications such as sepsis was very low (usually <1%) with both approaches. The short-term use of antibiotic prophylaxis with TRBx is a downside, but there are no data showing that this leads to a higher rate of multiresistant infections later on. However, patient discomfort is crucial because it may result in rejection of follow-up biopsy, for example as mandated in an active surveillance protocol. In addition, TRBx is easy to perform and the cost of the additional equipment for TPBx is not justified by data.

In conclusion, future discussions regarding prostate biopsy should not focus on the biopsy route but on more important questions such as whether to perform a biopsy at all. New data on primary staging via prostate specific membrane antigen (PSMA) positron emission tomography

(PET) suggest that in the near future, aggressive PCs—which are the only cases needing immediate diagnosis and treatment—may best be seen on PSMA PET imaging [7,8]. RCTs are difficult to perform and should be reserved for game-changing clinical questions.

Conflicts of interest: The author has nothing to disclose.

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Re: An In Situ Engineered Chimeric IL-2 Receptor Potentiates the Tumoricidal Activity of Proinflammatory CAR Macrophages in Renal Cell Carcinoma

Jing W, Han M, Wang G, et al

Nat Cancer 2025;6:838–53

Experts' summary:

Jing et al [1] developed a modular strategy to overcome the phenotypic reprogramming of chimeric antigen receptor (CAR) macrophages within the immunosuppressive microenvironment of renal cell carcinoma (RCC). By delivering circular RNAs encoding anti-CA9 CAR and a synthetic IL-2R–TLR4 chimeric receptor via mannose-modified lipid nanoparticles, combined with local IL-2 administration via an injectable hydrogel, the authors successfully promoted M1 polarization of macrophages, enhanced phagocytosis of $CA9^{+}$ tumor cells, and improved T-cell infiltration and cytotoxic activity. This approach effectively inhibited tumor growth, metastasis, and recurrence in orthotopic, postoperative, and humanized RCC models, highlighting the potential of macrophage-based immunotherapy in RCC.

Experts' comments:

The application of CAR cell therapies, including T-cell (CAR-T), NK cell (CAR-NK), and macrophage (CAR-M) options, is rapidly expanding beyond hematological malignancies and offering new therapeutic options for solid tumors. Despite biological and technical challenges, CAR-based strategies hold great promise for improving tumor specificity, enhancing immune-cell infiltration, and overcoming the immunosuppressive tumor microenvironment (TME), which collectively remain key obstacles in the treatment of solid tumors [2].

The heterogeneity of the TME across solid tumors may inform rational selection of CAR cell therapies. It is well recognized that the abundance and composition of infiltrating lymphoid and myeloid cells vary considerably among tumor types, and influence both disease progression and response to immunotherapy. For example, in clear-cell RCC (ccRCC), in addition to abundant lymphocyte infiltration, there is substantial presence of tumor-associated macrophages that actively shape the immunosuppressive TME. However, the optimal application of CAR-T, CAR-NK, or CAR-M therapies on the basis of distinct immune landscape features remains to be defined. Further investigation into the relationship between TME characteristics and CAR cell efficacy will be essential to optimize treatment strategies and improve clinical outcomes in solid tumors.

The combination of CAR cell therapies with immunomodulatory or conventional therapies represents a promising approach to enhance antitumor efficacy. Jing et al [1] demonstrated that IL-2 signaling can be harnessed via a synthetic receptor to induce macrophage polarization